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The effects of mucilages of three different potato starches on the brittle fracture tendency of paracetamol tablets

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ABSTRACT

The effect of mucilages of three potato starches with maize starch mucilage on ameliorating the brittle fracture index of paracetamol tablets has been studied. Three potato starches were extracted using standard procedures. The starches were subjected to microscopy. Granules from their 5 %w/v binder solutions were evaluated for flow properties and the tablets formulated for tablet parameters. Brittle Fracture Indices (BFI) of the tablet formulations were determined by making two batches of tablets, one batch with centre holes and the other regular "blind" tablets. A comparison was made between the BFI values of the tablets made with the various potato starch mucilages and those made with maize starch mucilage. Granules and tablets formulated with the potato and maize starch mucilages met official compendial specifications and were comparable in granule flow properties, tablet weight variation, crushing strength, friability, disintegration times and dissolution rate. The brittle fracture indices of the tablets were not directly proportional to their tensile strengths and disintegration times. The rank order of BFI of the paracetamol tablets based on the mucilage type was: maize starch > Irish potato starch > sweet white potato starch > sweet pink potato starch. The potato starch mucilages at 5 %w/v concentration gave paracetamol tablets of acceptable BFI as well as acceptable dissolution profiles. The potato starch mucilage reduced the brittle fracture tendency of the paracetamol tablets more than the maize starch mucilage. Hence the potato starch mucilages could be used as alternatives to maize starch mucilage, especially where faster disintegration is required of the tablets.

INTRODUCTION

Brittle fracture tendency of tablets is the tendency of tablets to cap or laminate during ejection from the tableting machine dies. It is a problem in the pharmaceutical industry as tablets in which this occurs have to be rejected or reprocessed leading to increased cost of production. The tendency for a tablet to fracture may be due to insufficient binder, a high plastoelasticity of the tableting base, and process factors such as excessive compression pressures and over drying of granules/powders [1].

Brittle fracture index (BFI) measures the ability of a material to relieve stress by plastic deformation around a defect. Causes of brittle fracture include, low density regions in the tablet, presence of entrapped air and predominance of elastic materials in the tablet. Low density regions are associated with uneven consolidation of the tablet during compaction [2].

Low density regions constitute weak points in the tablets which result in cracks and when the tablet is subjected to die wall pressure, the cracks are propagated. Sudden elastic recovery following tablet ejection from the die has been implicated as a possible cause of brittle fracture, supported by the evidence of direct correlation between the plasto-elasticity of materials and the BFI of resulting tablets [3]. Thus, plastic materials are less prone to brittle fracture when compared with elastic materials. Plastic materials ameliorate brittle fracture because they deform readily under stress to relieve the stress that would have concentrated at the edge of the void [2,4]. Those materials that relieve stress rapidly are less likely to cap or laminate. The brittleness test is based on the Griffith fracture theory which states that the energy stored at the tip of a crack must just exceed the

energy required to form two new surfaces resulting from the propagation of the crack, for crack growth to occur. Hiestand *et al*. showed that when compacts are made with a small axially oriented round hole at their centre, the compact is nearly always weakened [4]. Studies have shown that BFI is affected by compression speed and pressure. It is also affected by the nature and concentration of binding agents [5-7].

Starches are one of the native excipients used extensively in tablet formulation either as binders, disintegrants or lubricants. Maize starch is the most common of the starches used, however other sources have been explored [8-11]. Potato starch from the tubers of Irish potato (*Solanum tuberosum* L) is one of the official starches recommended by BP (2003) for pharmaceutical industries while sweet potato (*Ipomoea batatas* L) starches have also received considerable attention from researchers [8,11,12]. The low amylose content of these starches (10-30 %) [13] makes them ideal as pharmaceutical excipients [7]. The main objective of this study was to compare the effect of various locally sourced potato starch binders with maize starch mucilage binder in ameliorating the brittle fracture index of paracetamol tablets.

MATERIALS AND METHODS

Materials

Maize starch BP (Ganone GmbH Schonfeld Straβe, Rosenheim, Germany), Lactose BP (May and Baker, Nigeria), Magnesium stearate and Talc (International Co. Ltd. Anhui, China), Irish potato (*Solanum tuberosum*), Sweet potato (*Ipomoea batatas*) white and pink varieties were purchased locally and their starches extracted in the laboratory. All sieves were BSS 1796 (Endecotts Ltd. London, England)

Methods

Extraction of starches

About 10 kg of the potatoes were washed with tap water, peeled, rewashed and diced into pieces, and then passed through a milling machine. The slurry was mixed with sufficient 0.035 %w/w sodium hypochlorite for 18 h. The resulting slurry was then strained through a muslin cloth into water in a basin and allowed to settle for about 6 h. The supernatant was decanted and the residue containing starch was washed several times with water to neutral pH. The resulting wet mass of starch was air-dried and later dried in a hot air oven at 60 °C. This procedure was carried out for the different species of potatoes.

Microscopy

The starch powder was thinly spread over a glass slide and viewed under a light microscope (Labo Microsystems GmbH, Germany) via a calibrated eyepiece and the sizes and shape of the particles were recorded at a magnification of 40 (MICAM 1.4, ScopeImage 9.0).

Preparation of binder mucilage

A 5-% mucilage of each starch sample was prepared by dispersing 5.0 g of starch powder in 10 mL distilled water and stirred to form a homogenous mixture. Boiling water was immediately poured into the mixture to form a paste and stirred vigorously. The boiling water was used to make the mucilage up to 100 mL volume [5,14].

Granulation

The wet granulation method of massing and screening was used in preparing all the batches of paracetamol granules using the quantities shown in Table 1. Four batches of granules were produced with each batch representing the starch mucilage used as binder solution viz; maize starch BP, Irish potato starch, sweet white potato starch and sweet pink potato starch. The paracetamol powder and lactose (filler) were carefully weighed into a mixer and dry mixed for 5 min. Half of the weighed amount of disintegrant (maize starch) was incorporated intragranularly to the powder mix in geometric proportions during the mixing.

Sufficient quantities of the binder solution (5 %w/v) required to form a wet mass was gradually added to the dry powder mix. The wet mass was passed through a 710 μm sieve mesh screen and the resulting granules dried at 60 °C for 30 min in a hot air oven (Gallenkamp, UK). The granules were rescreened through the same sieve and further dried for another 30 min. The dry granules were subjected to various analyses and thereafter the other half of the disintegrant, glidant and lubricant previously weighed and mixed in a mortar were added in geometric proportion and intimately mixed in readiness for compression.

Granule analysis

Bulk density

A 30 g quantity of the granules was poured gently into a 100 mL graduated measure. The volume of the granules was read and the bulk density calculated.

Tapped density

The measure containing the 30 g of the granules was tapped 100 times on a wooden platform. The volume was noted and used in calculating the tapped density.

Carr's index

The difference between the tapped and bulk density of the granules divided by the tapped density was calculated and the ratio expressed as percentage.

Hausner's ratio

The ratio of the tapped density to the bulk density of the granules was calculated as the Hausner's quotient.

True density

25 mL specific gravity bottle (glass pycnometer) was filled with liquid paraffin, cleaned of any residual liquid paraffin and weighed (a). The bottle was emptied, rinsed with acetone and dried. About 1 g (b) of the granules was poured into the bottle and then filled with liquid paraffin. It was weighed (c) after cleaning off the residual paraffin from the bottle. The various weights recorded were used to calculate the true density of the granules using Equation 1 [15-17]. The tests were carried out for all the starches in replicates.

$$\rho = b/[(a+b)-c]S \quad \text{----- 1}$$

Where ρ is the particle density of the starch and S is the specific gravity of liquid paraffin

Flow rate

An Erweka flow tester (Model: GT, GmbH, Germany) was used. The time taken for 50 g of the paracetamol granules to pass through its orifice was recorded. This was carried out in triplicate and the mean values recorded.

Angle of repose

The hollow tube method was used. A short hollow tube of 3 cm

in internal diameter sitting on a circular horizontal surface of same diameter was filled with granules. The tube was withdrawn vertically and excess granules allowed to fall off the edge of the circular horizontal surface. The height of the heap was measured. The angle of repose, θ, was calculated using Equation 2.

$$\theta = tan^{-1} (h/r) \text{ - - - - - } 2$$

Where h is the height of the heap of granules and r is the radius of the circular base

Compression of granules

Batches of the granules were compressed into tablets using a single punch tableting machine (F-3 Manesty Machines, UK) at a compression pressure of 30 arbitrary units. The die volume was adjusted to compress tablets of uniform weight by using granules weighing 660 mg. One hundred and twenty tablets were produced per batch with twenty of them having centre holes by using special tableting adaptors. The tablets were kept in air tight containers until evaluation.

Tablet evaluations

The following tests were carried out on the compressed tablets using standard procedures: tablet dimensions, tablet weight uniformity, tensile strength, friability, disintegration time and dissolution studies.

Dimensions

The thickness and diameter of each of ten tablets per batch of each binder variety were measured using a micrometer screw gauge and their mean values recorded.

Weight uniformity

The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed.

Friability

The weight of ten tablets was determined on the electronic balance. The tablets were then placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm which exposed the tablets to rolling and repeated shock resulting from free fall within the apparatus. After four minutes, the tablets were brought out, dedusted and reweighed. The weight was then recorded and friability calculated as percentage loss in weight.

Tensile strength

The tensile strength (T) of normal tablets and the apparent tensile strengths (T_o) of the compromised tablets with holes of ten tablets per batch were determined by diametric compression using the hardness tester (Campbell Electronics, Model HT-30/50, India) and applying Equation 3 [18].

$$T = 2F/\pi dh \text{ - - - - - } 3$$

Where T = Tensile strength in MN/m^2, F = Force in MN needed to cause diametral tensile failure or breaking force, d = Tablet diameter in m, h = Tablet thickness in m.

Determination of BFI

The BFI of the batches of tablets was obtained by comparing the tensile strengths of the tablets with a hole at their centre (which acts as a built-in stress concentration defect) with the tensile strengths of tablets without a hole. The brittle fracture index (BFI) was calculated using Equation 4.

$$BFI = 0.5 (T/T_o - 1) \text{ - - - - - } 4$$

Where: T_o and T are the tensile strengths of tablets with and without a centre hole respectively. The centre hole (≤ 0.6 mm) is a built-in model defect to simulate actual void formed in the tablet during compression.

Disintegration time

The disintegration times of six tablets per batch of the tablets were determined in distilled water at 37 ± 2 °C using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean disintegration time was recorded.

Dissolution studies

The dissolution profiles of the paracetamol tablets were determined using the BP basket method for the various batches of the tablets (Caleva ST7, UK). A dissolution medium of 900 mL of 0.1M HCl solution maintained at 37 ± 0.5 C with a basket revolution of 50 rpm was used. A 5 mL volume of dissolution medium was withdrawn at various intervals and replaced with an equivalent volume of fresh dissolution medium maintained at same temperature ((37 ± 0.5 °C)). The samples were filtered and diluted with an equal volume of 0.1M HCl. This was continued for 60 min. The absorbances of the resulting solutions were measured at max of 245 nm (T70, PG Instruments Ltd, USA). The concentration and the percentage of drug release at each time interval was determined using the equation from the standard calibration plot obtained from the pure drug. A minimum of triplicate determinations was carried out for all experiments and the results were recorded as mean ± SD.

Statistical analysis

The data were subjected to the student's t-test at 5-% level of significance.

RESULTS

Microscopy

Microscopic examination of the starch particles showed polymodal particles with shapes ranging from round and irregularly shaped polyhedron granules of maize starch BP (Figure 1a) with size range of 2.0 - 4.0 µm to round and irregularly shaped polygonal particles of sweet white potato starch (Figure 1b) with size range of 30 - 70 µm to oval or elliptical shape of Irish potato starch (Figure 1c) with size range of 32 - 128 µm and the round, oval, polygonal and polyhedral particles of sweet pink potato starch. (Figure 1d) with size range of 3 - 11 µm.

Table 1. : Formula of prepared paracetamol tablets

Ingredients	Quantities	
	Per tablet	Per batch
Paracetamol	500 mg	50 g
Lactose	50 mg	5 g
Binder solution (5 %w/v)	qs	qs
Maize starch	50 mg	5 g
Magnesium stearate	0.5 %w/w	0.5 %w/w
Talc	0.5 %w/w	0.5 %w/w

Table 2. : Some physical properties of the paracetamol granules

Parameters	Mucilage type			
	Irish potato starch	Sweet white potato starch	Sweet pink potato starch	Maize starch BP
Bulk density (g/cm^3)	0.400	0.364	0.392	0.435
Tapped density (g/cm^3)	0.417	0.385	0.408	0.465
Flow rate (g/sec)	3.95	3.77	3.73	4.61
Angle of repose (°)	23.8	15.54	13.88	20.14
Hausner's ratio	1.04	1.06	1.04	1.07
Carr's index (%)	3.85	5.66	3.85	6.54

Table 3. : Some physical properties of the paracetamol tablets.

Starch mucilage	Weight (g)	Friability (%)	Diameter (mm)	Thickness (mm)	Disintegration time (sec)
Maize	0.63 (0.01)	1.59 (0.03)	12.47 (0.06)	4.61 (0.03)	100
Irish potato	0.66 (0.03)	1.47 (0.07)	12.55 (0.02)	4.90 (0.07)	70
Sweet white potato	0.66 (0.02)	0	12.55 (0.01)	4.76 (0.02)	65
Sweet pink potato	0.64 (0.02)	1.56 (0.04)	12.54 (0.04)	4.74 (0.03)	107

SD values are listed in parentheses

Table 4. : Brittle fracture indices of the paracetamol tablets

Starch mucilage	Crushing strength (N)		Tensile strength (MN/m^2)		BFI
	Tablets		Tablets		
	Hollow	Blind	Hollow	Blind	
Maize	51.98 (0.57)	57.38 (0.86)	5.76 x 10^5 (0.02)	6.36 x 10^5 (0.10)	0.052
Sweet white potato	57.87 (1.42)	60.42 (1.23)	6.17 x 10^5 (0.02)	6.44 x 10^5 (0.22)	0.022
Sweet pink potato	57.38 (1.40)	58.16 (1.20)	6.15 x 10^5 (0.22)	6.23 x 10^5 (0.23)	0.007
Irish potato	50.02 (0.32)	52.77 (0.75)	5.18 x 10^5 (0.01)	5.47 x 10^5 (0.05)	0.027

SD values are listed in parentheses

Granule properties

Bulk properties

Results of the bulk and tapped densities of the granules are shown in Table 2. The sweet white potato granules exhibited the highest volume reduction due to close packing, while the maize starch granules exhibited the lowest volume reduction. Thus, due to the applied tapping pressure, the polygonal shapes coupled with the small particle size of the sweet white potato starch permitted closer packing of particles than the round and irregularly shaped polyhedron granules of the maize starch. The close packing (packing fraction) of the starch granules followed the rank order: sweet white > sweet pink > Irish > maize.

Flow properties

The Hausner ratios, Carr's indices and angles of repose (Table 2) obtained in this study indicated that the paracetamol granules had excellent flow properties. The values obtained for Carr's index ranged from 3.85 - 6.54 while those of Hausner ratio ranged from 1.04 - 1.07 and the angles of repose ranged from 13.88 - 23.80°.

Tablet properties

Dimensions

Although the BP and USP do not insist on a standard weight for official tablets, but they do specify their diameter. Though tablet thickness is not directly controlled, most manufacturers in practice make uncoated tablet of thickness equal to half the diameter. The BP (2002) permits some slight deviation usually ± 5 % from the mean diameter [19]. The values obtained in this study (Table 3) were within the range for good tablets. The relative standard deviations (RSD) ranged from 0.1 - 0.5 %.

Uniformity of weight

Variation in weights of individual tablets could be attributed to non-uniform powder or granule flow, resulting in uneven filling of the dies. BP (2003) states that not more than two of the individual weights of the 20 tablets should deviate from the average weight by more than ± 5 % and none should deviate by

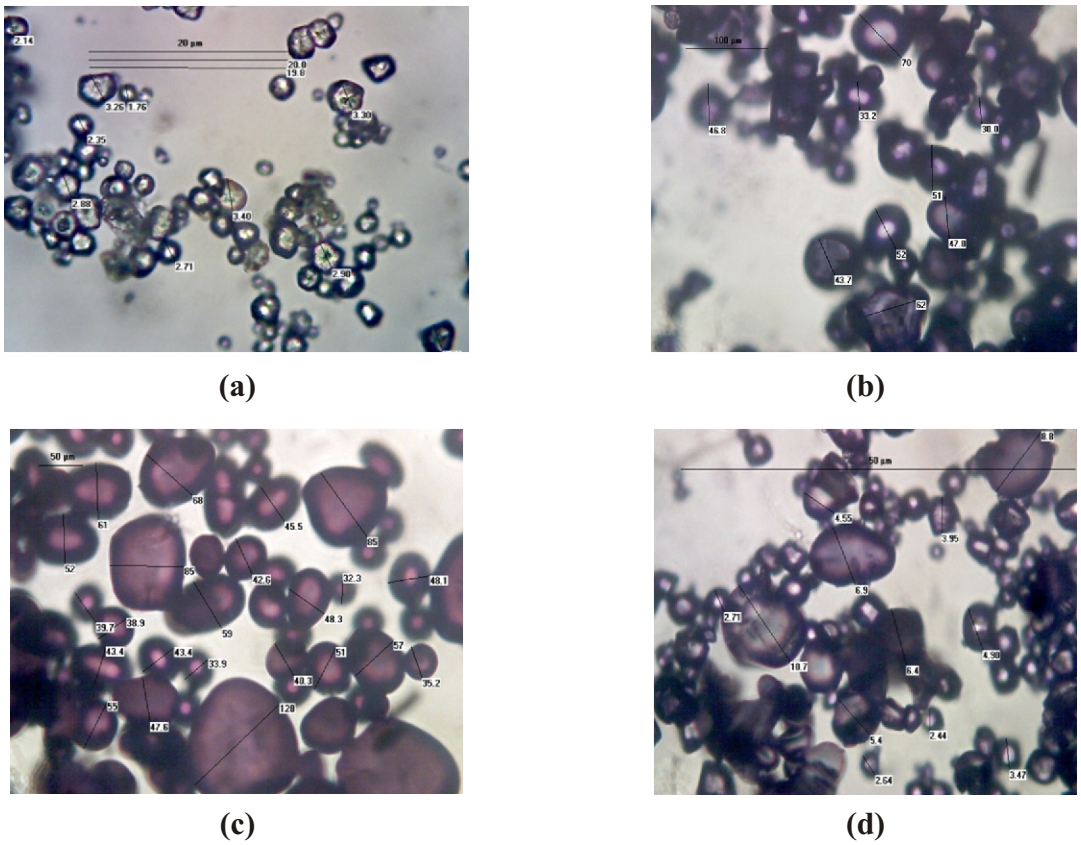

Fig 1. Microscopy of Maize starch (a), Sweet white potato starch (b), Irish potato starch (c) and Sweet pink potato starch (d). Magnification: X40

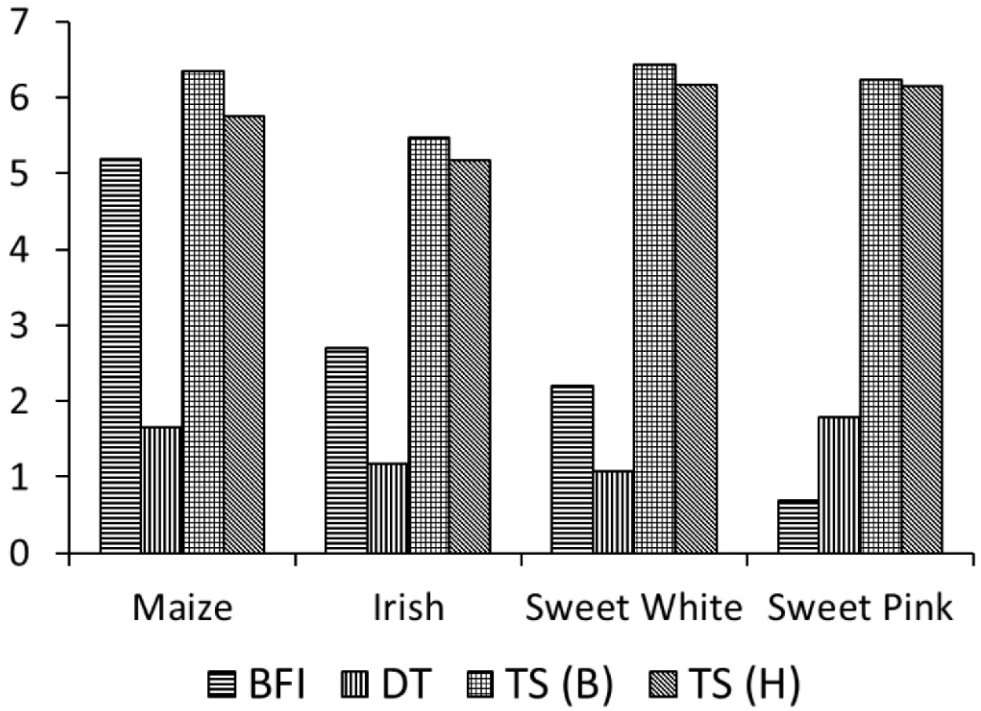

Fig 2. Comparisons of the brittle fracture indices (BFI), disintegration times (DT) and tensile strength of the blind (TS (B)) and hollow (TS (H)) tablets

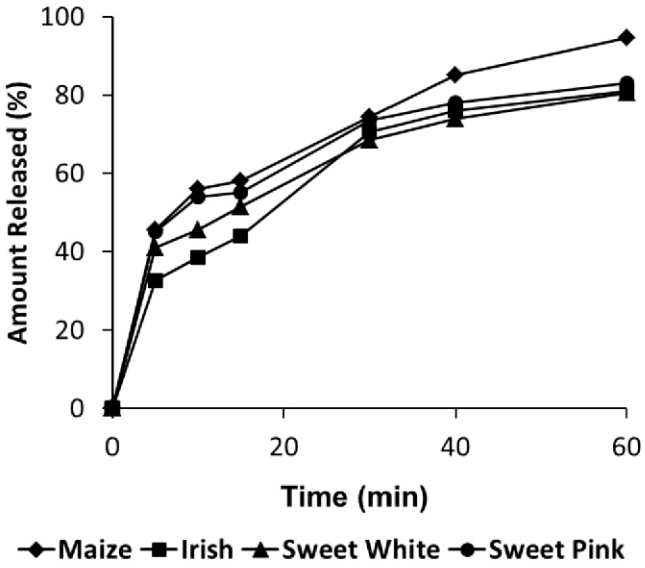

Fig 3. Dissolution profiles of the paracetamol tablets.

more than ± 10 % [20]. The weights of the tablets in all the batches (Table 3) met the official specification with values ranging from 632 - 659 mg and the variations were not more than ± 4 % of the calculated mean weight (655 mg).

Friability

Friability is related to the hardness of the tablet and it is the tendency of tablets to powder, chip or fragment. It can negatively affect the elegance, appearance and consumer acceptance of the tablet. A 1 % loss is generally considered the upper limit for tablets formulated by wet granulation [21], but a 2 % loss is permissible especially for large tablets prepared by direct compression. The values in this study (Table 3) were within the acceptable range. Friability values ranged from 0 - 1.59 %.

Disintegration times

All the formulated tablets disintegrated within 15 min (Table 3) as specified in BP (2003) [20] for uncoated tablets, but the results showed a reduction in the disintegration times in the rank order of binder type thus; sweet pink potato starch > maize starch > Irish potato starch > sweet white potato starch.

Crushing strength and BFI

Some of the factors that may affect the crushing strength (hardness) of a tablet include force of compression, binder concentration and method of granulation. A hardness of about 5 - 8 kgf (49.033 - 78.45 N) is acceptable for tablets [21]. The hardness values of the formulated tablets ranged from 5.38 - 6.16 kgf (52.77 - 60.42 N) i.e. within acceptable limits (Table 4). Sweet white potato binder produced the hardest tablets followed by the sweet pink potato binder, the maize starch binder, and then the Irish potato binder in that order. Their calculated tensile strengths also follow this order.

The brittle fracture indices of the tablets were not directly proportional to their tensile strengths (Figure 2). BFI values have a range of 0 (no fracture tendency) to 1 (maximal fracture tendency) [4]. The rank order of BFI of the paracetamol tablets based on the mucilage type was: maize starch > Irish potato starch > sweet white potato starch > sweet pink potato starch.

Dissolution profiles

Figure 3 shows the dissolution profiles of the formulated paracetamol tablets. The dissolution pattern agreed with the disintegration-dissolution theory, which indicates that disintegration usually plays a vital role in the dissolution process since it determines to a large extent, the area of contact between the solid and liquid [6]. However, all the batches of the tablets formulated passed the BP (2003) dissolution test for tablets, which specifies that at least 70 % of the drug should be in solution after 30 min [20].

DISCUSSION

Brittle fracture during tableting is a direct consequence of stress (due to die wall pressure) concentrating at the edge of voids or low density pockets which are weak points in the tablet and from which cracks emanate during decompression (i.e. withdrawal of the upper punch pressure). Plastic deformation of particles in the tablet can relieve the stress and thus ameliorate brittle fracture. Binders impact plasticity to tablet formulation and thereby ameliorate brittle fracture tendency [3]. Starches being the most common binders used in tablet formulations are meant to lessen considerably tablet fracture.

The potato starches studied when compared with maize starch exhibits a superior capacity to ameliorate brittle fracture in paracetamol tablets. Their BFI values implies paracetamol tablets made with maize starch mucilage have a higher tendency to cap and laminate during ejection from the die than the tablets made with Irish potato starch mucilage which in turn will have a greater tendency to fracture than those tablets made with sweet white potato starch mucilage. Tablets made with sweet pink potato starch mucilage have the lowest tendency to fracture than the tablets because of its low BFI value.

This observation implies that the potato starches compared with the maize starch promoted a greater plastic deformation of the granule particles during compaction. Plastic deformation increases the area of particle-particle contact and cohesion leading to the formation of hard tablets [22].

Accordingly, the crushing strengths of the tablets from the potato starches show that they were harder than those from maize starch. Uhumwangho *et al.*, [23] obtained similarly result with cassava and cocoyam starches where tablets from these starches were harder than those from maize starch and also had lower BFI values.

Tablet hardness is affected by a number of factor during tablet production; e.g the type of binder, binder concentration and compression pressure. In order to alleviate the problem of tablet fracture during manufacture, these factors must be taken into consideration to produce a tablet of acceptable hardness because an overly hard tablet may be not disintegrate and its drug content will not be available for dissolution and absorption.

CONCLUSION

Mucilages of the potato starches at 5 %w/v concentration used as binder gave tablets of acceptable BFI as well as acceptable dissolution profiles. This investigation may suggest that a change from maize starch mucilage as binder to the mucilage of any of the potato starches would lead to a decrease in the tensile strength, disintegration times and the brittle fracture tendencies of paracetamol tablets. Hence, the mucilage of any of the potato starches could be used as alternatives to maize starch mucilage in the formulation of paracetamol tablets especially where faster disintegration is required.

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